Matt Sauder

Full Progress Report

06.21.19

THE ISSUE...

Xu_orgLett_2011 (Au-cat):

200 μmol scale —

141.7 mg Selectfluor ($5.80/g) = $0.89
33.6 mg $NaHCO_3$ ($0.09/g) = $0.00
3.7 mg $Ph_3PAuNTf_2$ ($308.50/g) = $1.14
2 mL MeCN ($0.13/mL) = $0.25
(N_2, rt, 2hr, 81% yield) **$2.22**

V.S. my rxn

200 μmol (65 mg) scale — (2.6× scale of 25 mg rxns)

85.0 mg Selectfluor ($5.80/g) = $0.49
75.7 mg NFSI ($14.63/g) = $1.11
54.5 mg $Me_3Pyr^{\oplus}BF_4^{\ominus}$ ($24.66/g) = $1.34
60.9 mg $Cl_2Pyr^{\oplus}BF_4^{\ominus}$ ($26.20/g) = $1.60 — ★

33.6 mg $NaHCO_3$ ($0.09/g) = $0.00 — ★

0.5 eq
19.5 mg $AgBF_4$ ($19/g) = $0.37 — ★
25.7 mg AgOTf ($9/g) = $0.23
0.8 eq
30.5 mg CuI* ($8/g) = $0.24
57.9 mg $Cu(OTf)_2$* ($13/g) = $0.75

2 mL MeCN ($0.13/mL) = $0.25 — ★

$0.98 — $2.60
(44%) (117%)
★ = $2.22 (100%)

Cost of F+ Sources:					
F+	$/g	Reactivity (Rozatian)	Moisture Sens	Solubility MeCN	Notes
Selectfluor	$ 5.80	1		poor	
NFSI	$ 14.63	10^-4		high	side rxns
Me3pyrBF4	$ 24.60	10^-6		good	
Cl2pyrBF4	$ 26.20	0.3	√	good	
Me3pyrOTf	$ 26.80	10^-6		good	
FpyrOTf	$ 30.40	10^-5			
Cl2pyrOTf	$ 40.40	0.2	√	good	
FpyrBF4	$ 46.25	10^-5			
Synfluor	$ 52.20	0.1	√		
Cl5pyr(BF4)	X	90			eats glass
Accufluor	X	1.5			

	TRIED	DON'T HAVE	HAVE
LA	$AgBF_4$ $Cu(OTf)_2$	$FeCl_2$ AgI PtCl $AgNTf_2$ $B(OTf)_3$ Ag_2ClO_4 DABCO? AgPF6 $ce(OTf)_3$ $Er(OTf)_3$ $Fe(OTf)_3$ $CuNTf_2$ $Yb(OTf)_3$ $CuOTf \cdot MeCN)_4$	$TiCl_4$ Cs_2CO_3 $AgOTs$ $PtCl_3$ $InCl_3$ $SnCl_4$ $Zn(OTf)_2$ $BF_3 \cdot$ EtOEt $AgOTf$ Ag_2SbF_6 $Sc(OTf)_3$ Ag_2NO_3 CuTc CuI
$F^{\oplus}$	Selectfluor NFSI $Me_3Pyr^{\oplus}$ $Cl_2Pyr^{\oplus}$	F-Tagnis [see F+ table]	
$CF_3^{\oplus}$	Togni II Umemoto II	Umemoto I?	TMS-CF_3*
Solvent	THF MeCN		Toluene [*$NaHCO_3$] DMF DMSO $MeNO_2$
Base	$NaHCO_3$	$CO_3^{\ominus}$ $AcO^{\ominus}$ $CN^{\ominus}$ $NO_2^{\ominus}$ $HS^{\ominus}$ $H_2PO_4^{\ominus}$ $SO_4^{\ominus}$	

K_2CO_3 in MeCN*

May use
Will use eventually
Planning to use

BASE SOLUBILITY:

Na_2SO_4 in Tol — (r.t / 50°) — translucent
$MgSO_4$ in MeCN/Tol — (rt / 50°) — suspension
KH_2PO_4 in tol — (rt, 50°C) — gel?
K_2HPO_4 in tol — (r.t only) — translucent
$NaOAc$ in MeCN — (r.t, 50C) — trans √√√
t-BuOK in tol — (r.t, 50°C) — trans

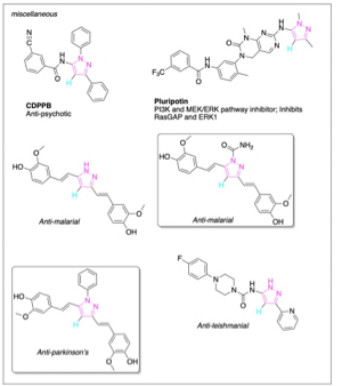
($NaHCO_3$ being used → not good solubility, goes away after 24h stir)

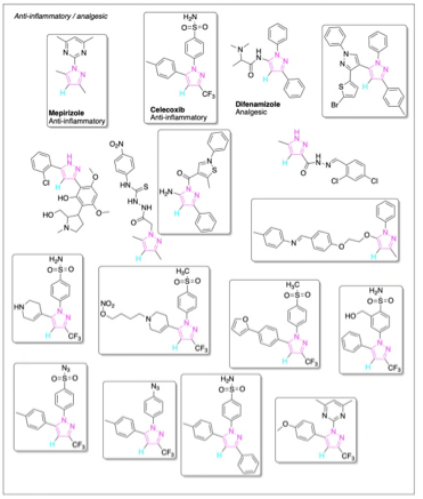
H2O | Select | base ***

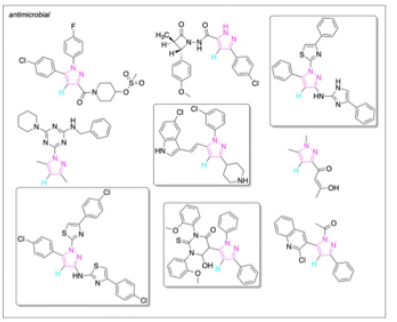
Options:

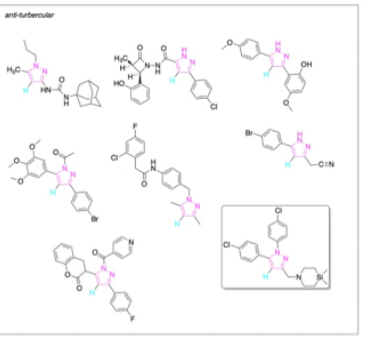
- We have to be very cautious of the price IF that's the big deal
  - → Xu_OrgLett_2011 tried Selectfluor/CuI/$NaHCO_3$ in MeCN with 15%
  - → Li_Synlett_2016 tried iPr_2NH (2eq) & grinding w/o $F^{\oplus}$
  - → Zora_JOC_2019 tried CuI/NEt_3 w/o $F^{\oplus}$
- We try to use base / $F^{\oplus}$ w/o LA cat.
  - → See base solubility (Sonpad says sometimes it still works if suspension) } see optimization table
  - → I want to try H_2O → Selectfluor/Base/Sm (sonicated) } see optimization table
- We use Au-Cat synthesis to make potentially pharmaceutically active compounds replacing pyrazole-H w/ pyrazole F
  - → See potentially pharm.-active compounds (below is screenshot, dropbox is Chemdraw file)

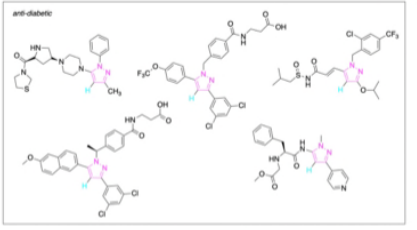
Potential Therapeutic Targets with Xu Au Paper Synthesis:
(boxed molecules avoid -NH- pyrazoles and carbonyls)

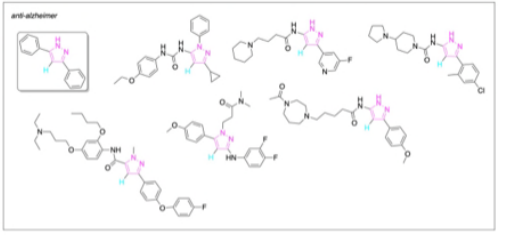


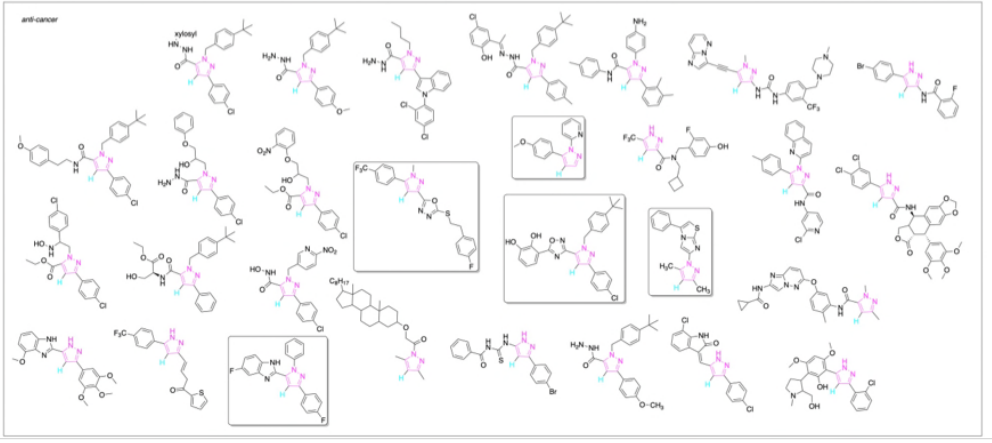


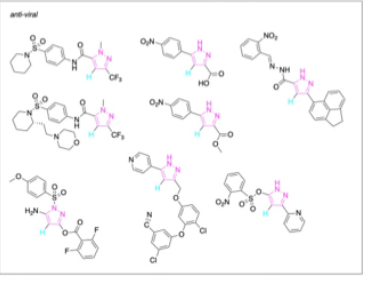






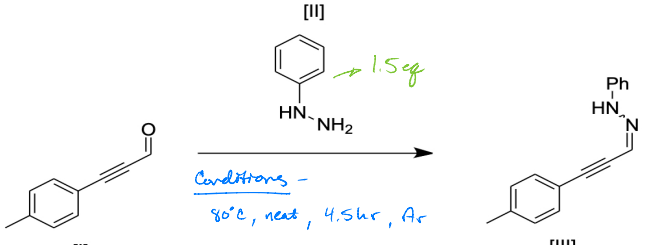






MS-001-020-1:

Reaction Scheme:

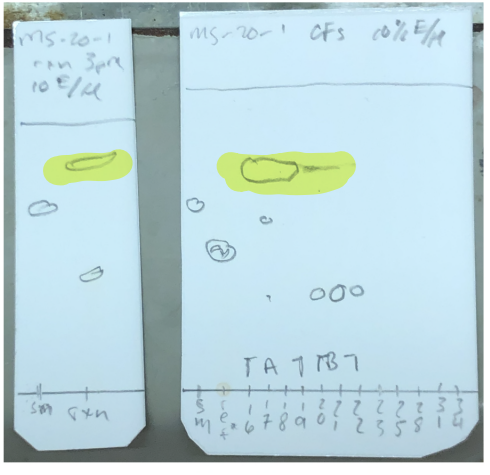


192.4 mg scale

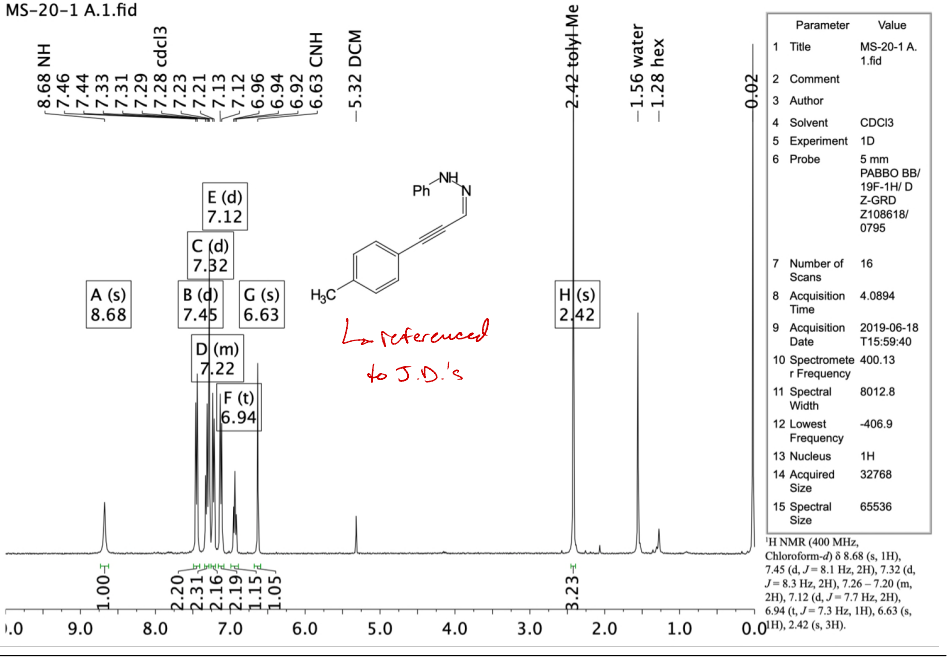
294.6 mg (94% yield)

TLC:

TLC 1 - rxn & CFs (10% E/H)



NMRs:



	Parameter	Value
1	Title	MS-20-1 A. 1.fid
2	Comment	
3	Author	
4	Solvent	CDCl3
5	Experiment	1D
6	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0795
7	Number of Scans	16
8	Acquisition Time	4.0894
9	Acquisition Date	2019-06-18 T15:59:40
10	Spectrometer Frequency	400.13
11	Spectral Width	8012.8
12	Lowest Frequency	-406.9
13	Nucleus	1H
14	Acquired Size	32768
15	Spectral Size	65536

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.26 – 7.20 (m, 2H), 7.12 (d, *J* = 7.7 Hz, 2H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.63 (s, 1H), 2.42 (s, 3H).

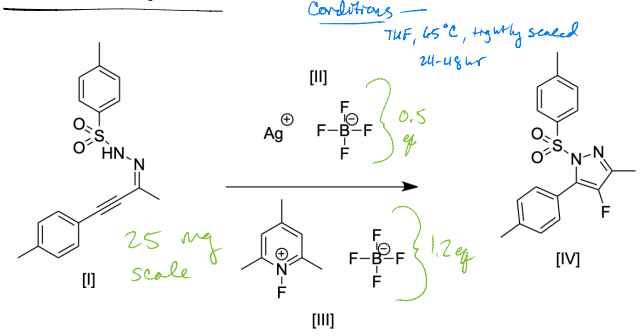
NOTES:

* Now have made all 4 SMs

SM-01	~340 mg
~~SM-02~~	~~~94 mg~~
SM-03	~180 mg
SM-04	~295 mg

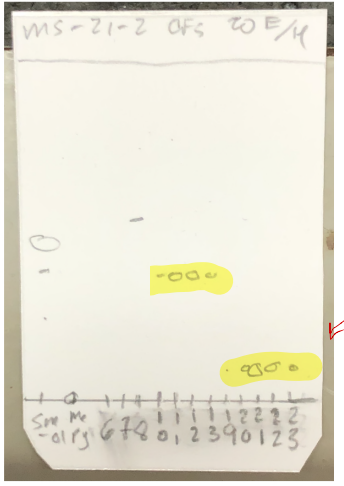
MS-001-021-2:

Reaction Scheme:



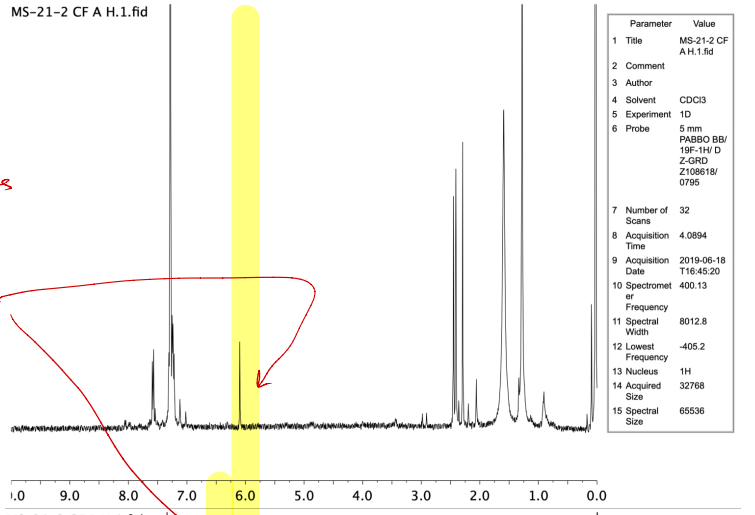
TLCs:

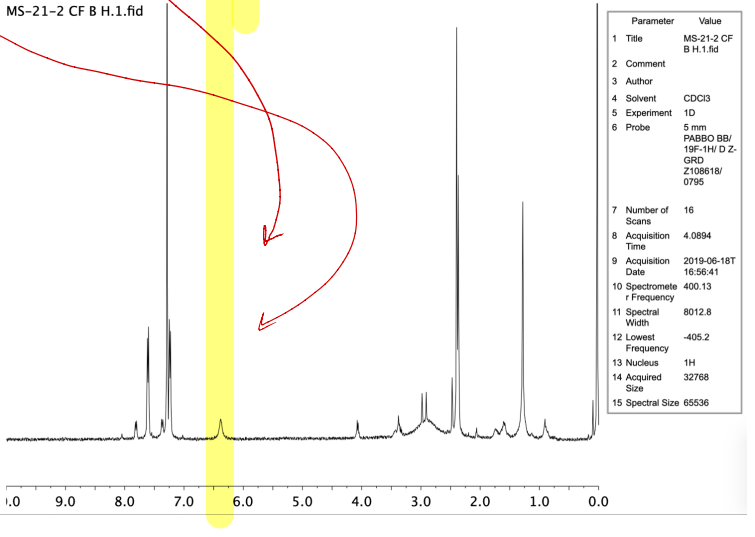
TLC 2 - column fractions (20% EA/HEX)



NMRs:

- No 19F-NMR peaks
- Submitted CFs to Shemba for mass
- Is this pyrazole?
- MS-21-3 CF is same as (B)

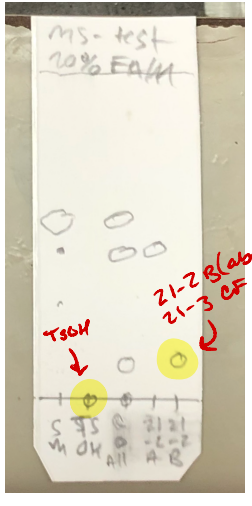

MS-21-2 CF A H.1.fid
Parameter Value
1 Title MS-21-2 CF A H.1.fid
2 Comment
3 Author
4 Solvent CDCl3
5 Experiment 1D
6 Probe 5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0795
7 Number of Scans 32
8 Acquisition Time 4.0894
9 Acquisition Date 2019-06-18 T16:45:20
10 Spectrometer Frequency 400.13
11 Spectral Width 8012.8
12 Lowest Frequency -405.2
13 Nucleus 1H
14 Acquired Size 32768
15 Spectral Size 65536
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0


MS-21-2 CF B H.1.fid
Parameter Value
1 Title MS-21-2 CF B H.1.fid
2 Comment
3 Author
4 Solvent CDCl3
5 Experiment 1D
6 Probe 5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0795
7 Number of Scans 16
8 Acquisition Time 4.0894
9 Acquisition Date 2019-06-18T 16:56:41
10 Spectrometer Frequency 400.13
11 Spectral Width 8012.8
12 Lowest Frequency -405.2
13 Nucleus 1H
14 Acquired Size 32768
15 Spectral Size 65536
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0

MS-001-021-3:

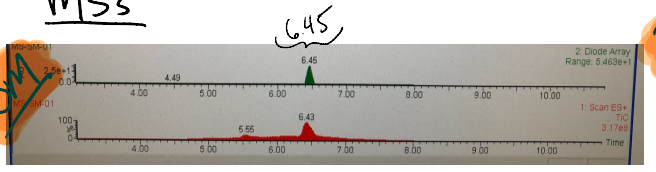
TsOH Comparison . . .

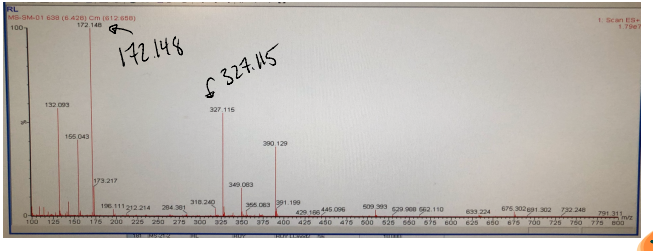
TLC:



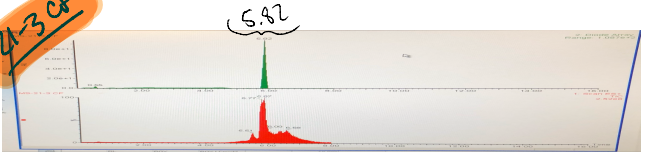
MSs

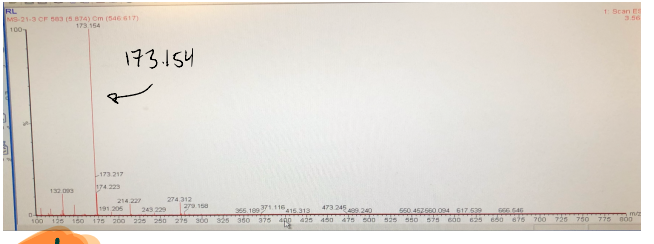
SM



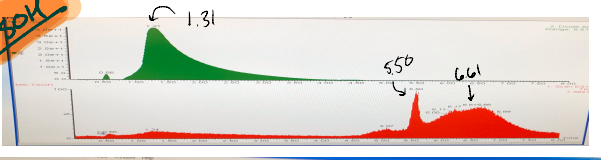


21-3 CF

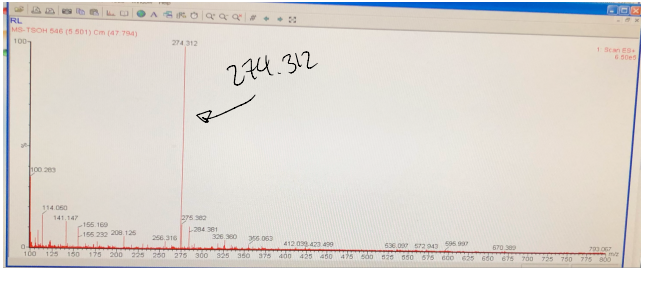




TsOH



☆ See Mass comparison chart in Matt's Folder for comprehensive list of possible masses (SM's & PR's)

→ weird Retention Time & Mass peak → 

(Shawba said it might be too concentrated, so I diluted it & resubmitted it)

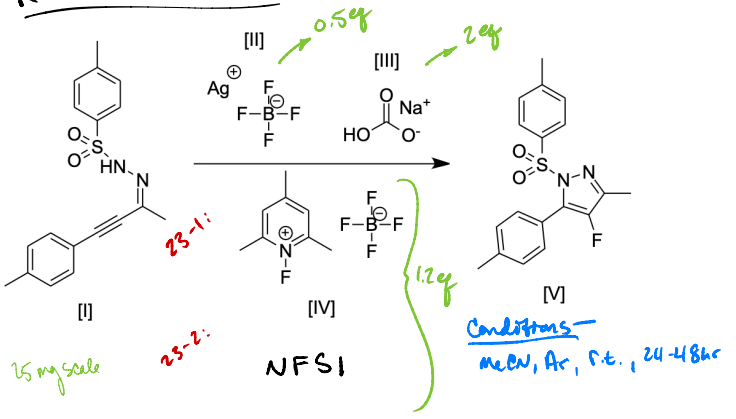
NMRs

☆ By NMR TS-OH looks fine, no peak around pyrazole peaks

(Note: TsOH·H_2O bottle, not "pure" TsOH)

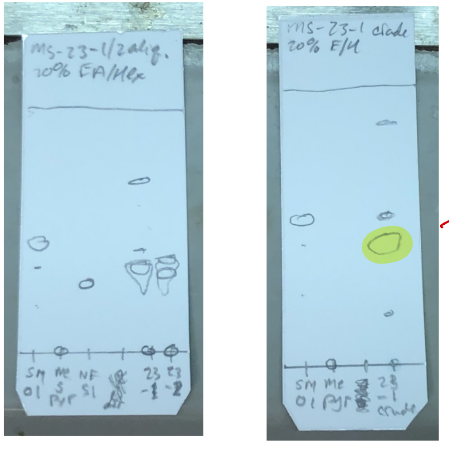
MS-001-023-1/2:

Reaction Scheme:



TLCs:

TLC 1 - rxn mixture (20% EA/HEX) TLC 2 - crude (20% EA/HEX)



NMRs:

* 23-1 aliquot ^{19}F-NMR

  δ = +16.64, -153.36, -217.12

  ↳ crude = NO PEAKS

  ↳ crude ^{1}H-NMR has sharp 6.09 peak (pyrazole?)

* 23-2 aliquot ^{19}F-NMR

  δ = -38.43 & -153.52

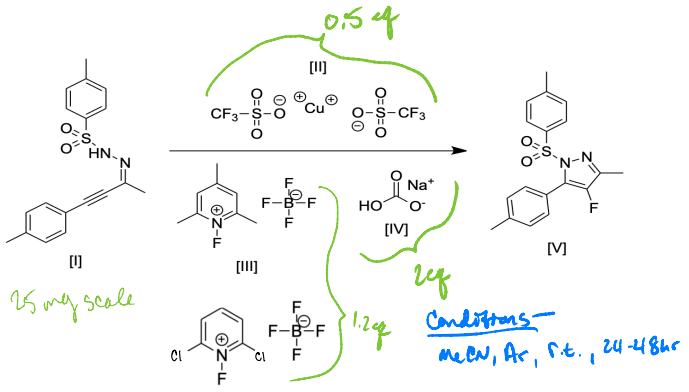
  ↓ NFSI ↓ BF_4^-

Notes:

- I submitted aliquot MS samples, yet to run
- $NaHCO_3$ not soluble, but "consumed" by 24 hr
- 23-1 changed to blue, 23-2 NO color change

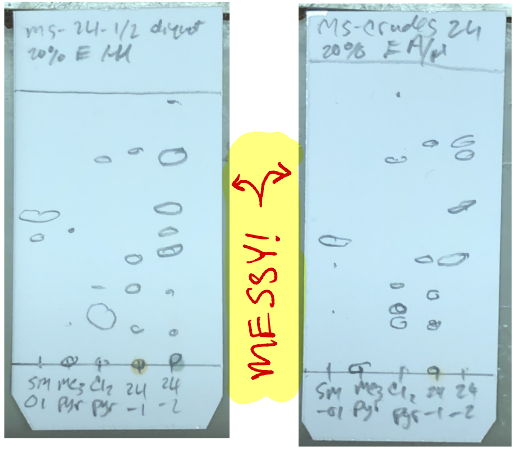
MS-001-024-1/2:

Reaction Scheme:



TLCs:

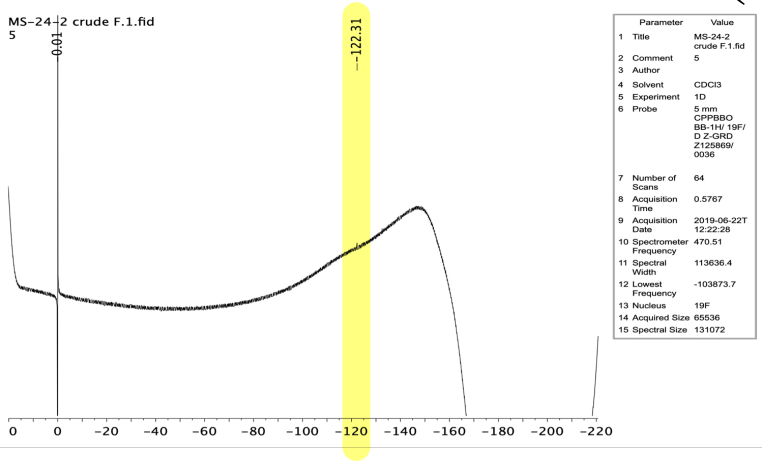
TLC 1 - rxn mixture (20% EA/HEX) TLC 2 - crude (20% EA/HEX)



NMRs:

* 24-1 aliquot δ = -78.74 & -151.90
  - ↓ OTf
  - BF_4
  - ↳ crude = no peaks

* 24-2 aliquot δ = -78.72, -122.62, -140.57 [small peaks]
  - ↳ crude = smallest peak at -122.31
  - ↳ crude ^1H = dilute but o/ 6.09 peaks (pyrazole?)



	Parameter	Value
1	Title	MS-24-2 crude F.1.fid
2	Comment	5
3	Author	
4	Solvent	CDCl3
5	Experiment	1D
6	Probe	5 mm CPPBBO BB-1H/ 19F/ D Z-GRD Z125869/ 0036
7	Number of Scans	64
8	Acquisition Time	0.5767
9	Acquisition Date	2019-06-22T 12:22:28
10	Spectrometer Frequency	470.51
11	Spectral Width	113636.4
12	Lowest Frequency	-103873.7
13	Nucleus	19F
14	Acquired Size	65536
15	Spectral Size	131072

Notes:

* submitted aliquots for mass, not run yet
* peak at -122?

Review:

1. Make a hard decision on our project
2. Can we find 4-pyrazole for reference
3. -122 peak in 24-1 interesting?
4. Plan next reactions [make on calendar]